PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Houtzager et al.

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PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend the above identified patent application as follows:

IN THE CLAIMS:

Claims 1-11, 13-15, 17-25, 27-30, and 32-44 are amended herein. All amendments are made without prejudice or disclaimer. All of the pending claims are presented, pursuant to 37 C.F.R. §§ 1.121(c)(1)(i) and 1.121(c)(3), in clean form below. Please enter these claims as amended. Also enclosed herewith is a marked-up version of the claims amended herein pursuant to 37 C.F.R. § 1.121(c)(1)(ii).

1. (Amended) A chimeric phage having a coat comprising a mixture of proteins, said mixture of proteins comprising:

a fusion protein wherein a proteinaceous molecule is fused to a functional form of a phage coat protein, and

a mutant form of said phage coat protein, wherein said mutant form is characterized in that a phage comprising no wild type phage coat protein from which said mutant form is derived and having a coat comprising said mutant form and no copies of said functional form is less infectious than a phage comprising no wild type phage coat protein from which said mutant form is derived and having a coat comprising said mutant form and at least one copy of said functional form.

2. (Amended) The chimaeric phage according to claim 1 wherein said phage coat protein comprises the g3 protein.

3. (Amended) The chimaeric phage according to claim 2 wherein said mutant form comprises a mutation in the Dl and/or the D2 region of said g3 protein.

4. (Amended) The chimaeric phage according to claim 3 wherein said mutation comprises a deletion of substantially all of said Dl and said D2 region of said g3 protein.

5. (Amended) The chimaeric phage according to claim 1 comprising a nucleic acid encoding said fusion protein.

6. (Amended) The chimaeric phage according to claim 1 wherein said chimaeric phage is derived from a M13, M13K07, VCSM13 or R408 phage.

7. (Amended) The chimaeric phage according to claim 1 wherein said proteinaceous molecule comprises a peptide, a protein, or a part, analogue or derivative of said peptide or said protein.

8. (Amended) The chimaeric phage according to claim 1 wherein said proteinaceous molecule comprises an antibody, a Fab fragment, a single chain Fv fragment, a variable region, a CDR region, or an immunoglobulin or a functional part of said Fab fragment, said single chain Fv fragment, said variable region, said CDR region or said immunoglobin.

9. (Amended) A chimaeric phage having a coat comprising a mixture of proteins, said mixture of proteins comprising:

a fusion protein wherein a proteinaceous molecule is fused to a phage coat protein, or to a fragment or derivative of said phage coat protein, and wherein said fusion protein is functional so as to render the chimaeric phage infectious, and

a mutant form of said phage coat protein wherein said mutant form is characterized in that a phage comprising no wild type phage coat protein from which said mutant form is derived and carrying said mutant form and no copies of said fusion protein is less infectious than a phage comprising no wild type phage coat protein from which said mutant form is derived and carrying in addition to said mutant form at least one copy of said fusion protein.

10. (Amended) The chimaeric phage according to claim 9 wherein said mutant form is characterized in that a phage comprising no wild type phage coat protein from which said mutant form is derived and carrying said mutant form and no copies of said fusion protein is non-infectious.

11. (Amended) The chimaeric phage according to claim 1 wherein said mutant form is further characterized in that a phage having a coat comprising said mutant form in the presence or absence of copies of said functional form is stable.

12. An infectious phage containing at least one copy of a mutant form of a phage coat protein, wherein said mutant form has lost the ability to mediate infection of a natural host by said infectious phage.

13. (Amended) A phage collection comprising:

the chimaeric phage according to claim 1, or

an infectious phage containing at least one copy of a mutant form of a phage coat protein wherein said mutant form has lost the ability to mediate infection of a natural host by said infectious phage.

14. (Amended) The phage collection according to claim 13 wherein said phage collection comprises a phage display library.

15. (Amended) A phage collection consisting essentially of:

the chimaeric phage according to claim 1, or

an infectious phage containing at least one copy of a mutant form of a phage coat protein wherein said mutant form has lost the ability to mediate infection of a natural host by said infectious phage.

16. A method for producing a phage particle comprising the steps of:

providing a host cell with a first nucleic acid encoding a fusion protein, said fusion protein comprising a proteinaceous molecule fused to a functional form of a phage coat protein,

providing said host cell with a second nucleic acid encoding a mutant form of said phage coat protein, said mutant form being characterized in that a phage comprising no wild type phage coat protein from which said mutant form is derived and having a coat comprising said mutant form and no copies of said functional form is less infectious than a phage comprising no wild type phage coat protein from which said mutant form is derived and having a coat comprising at least one copy of said functional form and wherein said host cell comprises an additional nucleic acid sequence encoding at least all other proteins, or functional equivalents thereof, that are essential for the assembly of said phage particle in said host cell, and

culturing said host cell to allow assembly of said phage particle.

17. (Amended) The method according to claim 16 wherein expression of said fusion protein and/or said mutant form is regulatable by altering the culturing conditions of said host cell.

18. (Amended) The method according to claim 16 wherein expression of said fusion protein and/or said mutant form is under the control of a regulatable promoter.

19. (Amended) The method according to claim 18 wherein said regulatable promoter comprises the AraC/BAD promoter or a functional equivalent of said AraC/BAD promoter.

20. (Amended) The method according to claim 16 wherein said additional nucleic acid sequence is provided by a helper phage to said host cell.

21. (Amended) The method according to claim 20 wherein said helper phage comprises said second nucleic acid.

22. (Amended) The method according to claim 16 wherein said fusion protein and said mutant form are encoded by separate nucleic acids, each comprising a unique selection marker.

23. (Amended) The method according to claim 22 wherein said separate nucleic acids each comprise a unique origin of replication.

24. (Amended) The method according to claim 22 wherein said separate nucleic acids each comprise codons that essentially do not permit a homologous recombination event between said separate nucleic acids.

25. (Amended) The method according to claim 16 wherein said phage particle comprises:
a chimaeric phage having a coat comprising a mixture of proteins, said mixture of proteins comprising:

a fusion protein wherein a proteinaceous molecule is fused to a functional form of a phage coat protein, and

a mutant form of said phage coat protein, wherein said mutant form is characterized in that a phage comprising no wild type phage coat protein from which said mutant form is derived and having a coat comprising said mutant form and no copies of said functional form is less infectious than a phage comprising no wild type phage coat protein from which said mutant form is derived and having a coat comprising said mutant form and at least one copy of said functional form, or

an infectious phage containing at least one copy of a mutant form of a phage coat protein wherein said mutant form has lost the ability to mediate infection of a natural host by said infectious phage.

26. A helper phage comprising a nucleic acid encoding phage proteins or functional equivalents of said phage proteins that are essential for the assembly of said helper phage, said nucleic acid encoding phage proteins further encoding a mutant form of a phage coat protein wherein said mutant form is characterized in that a phage comprising no wild type phage coat protein from which said mutant form is derived and having a coat comprising said mutant form and no copies of a functional form of said phage coat protein is less infectious than a phage comprising no wild type phage coat protein from which said mutant form is derived and having a coat comprising at least one copy of said functional form wherein said functional form is characterized in that it renders a phage particle carrying said functional form in its coat infectious and wherein said helper phage does not comprise a nucleic acid encoding said functional form.

27. (Amended) The helper phage according to claim 26 wherein said phage coat protein is the g3 protein.

28. (Amended) The helper phage according to claim 27 wherein said mutant form comprises a mutation in the D1 and/or the D2 region of said g3 protein.

29. (Amended) The helper phage according to claim 28 wherein said mutation comprises a deletion of substantially all of said D1 and said D2 region of said g3 protein.

30. (Amended) The helper phage according to claim 26 wherein said mutant form is further characterized in that a phage having a coat comprising said mutant form in the presence or absence of a copy of said functional forms is stable.

31. A method for producing a helper phage comprising the steps of:
providing a host cell with a first nucleic acid encoding a functional form of a phage coat protein,
providing said host cell with a second nucleic acid encoding a mutant form of said phage coat protein wherein said mutant form is characterized in that a phage comprising no wild type phage coat protein from which said mutant form is derived and having a coat comprising said mutant form and no copies of said functional form is less infectious than a phage comprising no wild type phage coat protein from which said mutant form is derived and having a coat comprising at least one copy of said functional form wherein said host cell comprises an additional nucleic acid sequence encoding at least all other proteins or functional equivalents thereof that are essential for the assembly of said helper phage in said host cell, and
culturing said host cell to allow assembly of said helper phage.

32. (Amended) The method according to claim 31 wherein said other proteins or functional equivalents thereof that are essential for the assembly of said helper phage in said host cell are encoded by said second nucleic acid.

33. (Amended) The method according to claim 31 wherein expression of said functional form and/or said mutant form is regulatable by altering the culturing conditions of said host cell.

34. (Amended) The method according to claim 31 wherein expression of said functional form and/or said mutant form is under the control of a regulatable promoter.

35. (Amended) The method according to claim 34 wherein said regulatable promoter comprises an AraC/BAD promoter or a functional equivalent of said AraC/BAD promoter.

36. (Amended) The method according to claim 31 wherein said phage coat protein is the g3 protein.

37. (Amended) The method according to claim 36 wherein said mutant form comprises a mutation in the Dl and/or the D2 region of said g3 protein.

38. (Amended) The method according to claim 37 wherein said mutation comprises a deletion of substantially all of said Dl and said D2 region of said g3 protein.

39. (Amended) The method according to claim 31 wherein said first nucleic acid and said second nucleic acid each comprise a unique selection marker.

40. (Amended) The method according to claim 31 wherein said first nucleic acid and said second nucleic acid each comprise a unique origin of replication.

41. (Amended) The method according to claim 31 wherein said first nucleic acid and said second nucleic acid comprise codons that essentially do not permit a homologous recombination event between said first nucleic acid and said second nucleic acid.

42. (Amended) The method according to claim 33 wherein said helper phage comprises a nucleic acid encoding phage proteins or functional equivalents of said phage proteins that are essential for the assembly of said helper phage, said nucleic acid encoding phage proteins further encoding a mutant form of a phage coat protein wherein said mutant form is characterized in that a phage comprising no wild type phage coat protein from which said mutant form is derived and having a coat comprising said mutant form and no copies of a functional form of said phage coat

protein is less infectious than a phage comprising no wild type phage coat protein from which said mutant form is derived and having a coat comprising at least one copy of said functional form wherein said functional form is characterized in that it renders a phage particle carrying said functional form in its coat infectious and wherein said helper phage does not comprise a nucleic acid encoding said functional form.

43. (Amended) A method for the enrichment of a first binding pair member in a repertoire of first binding pair members selected from the group consisting of an antibody, an antibody fragment, a single chain Fv fragment, a Fab fragment, a variable region, a CDR region, an immunoglobulin or a functional part of said antibody, said antibody fragment, said single chain Fv fragment, said Fab fragment, said variable region, said CDR region, or said immunoglobulin, said first binding pair member being specific for a second binding pair member, said method comprising the steps of:

contacting the phage collection according to claim 13 with material comprising said second binding pair member under conditions allowing specific binding,

removing non-specific binders, and

recovering specific binders, said specific binders comprising said first binding pair member.

44. (Amended) The method according to claim 43 comprising the additional steps of:

recovering from a phage a DNA sequence encoding said first specific binding pair member,

subcloning said DNA sequence in a suitable expression vector,

expressing said DNA sequence in a suitable host, and

culturing said suitable host under conditions whereby said first specific binding pair member is produced.

45. A nucleic acid molecule comprising a sequence encoding a mutant form of a phage coat protein, said mutant form being characterized in that a phage comprising no wild type phage coat protein from which said mutant form is derived and having a coat comprising said mutant form

and no functional form of said phage coat protein is less infectious than a phage comprising no wild type phage coat protein from which said mutant form is derived and having a coat comprising said mutant form and at least one copy of said functional form of said phage coat protein wherein said functional form is characterized in that it renders a phage carrying said functional form in its coat infectious.

REMARKS

The application is to be amended without prejudice or disclaimer as previously set forth, which should not be viewed as narrowing or limiting the claims. The amendments are sought to conform the application to a form more consistent with Office practice by removing multiple dependencies. It is respectfully submitted that no new matter has been added by the amendments. Should the Office determine that additional issues remain, which might be resolved by a telephone conference, it is respectfully invited to contact applicants' undersigned attorney.

Respectfully Submitted,

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Enclosure: Version With Markings to Show Changes Made

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

1.(Amended) A chimaeric phage having a coat comprising a mixture of proteins, said mixture of proteins comprising:

a fusion protein wherein a proteinaceous molecule is fused to a functional form of a phage coat protein, [said mixture further comprising]and

a mutant form of said phage coat protein, wherein said mutant form is characterized in that a phage, comprising no wild type phage coat protein front which said mutant form is derived and having a coat comprising said mutant form and no copies of said functional form, is less infectious than a phage, comprising no wild type phage coat protein from which said mutant form is derived and having a coat comprising said mutant form and at least one copy of said functional form.

2. (Amended) [A]The chimaeric phage according to claim 1[,] wherein said phage coat protein is the g3 protein.

3. (Amended) [A]The chimaeric phage according to claim 2[,] wherein said mutant form comprises a mutation in the Dl and/or the D2 region of said g3 protein.

4. (Amended) [A]The chimaeric phage according to claim 3[,] wherein said mutation comprises a deletion of substantially all of said Dl and said D2 region of said g3 protein.

5. (Amended) [A]The chimaeric phage according to [any one of claims 1-4]claim 1 comprising a nucleic acid encoding said fusion protein.

6. (Amended) [A]The chimaeric phage according to [any one of claims 1-5,]claim 1 wherein

said chimaeric phage is derived from a M13, M13K07, VCSM13 or R408 phage.

7. (Amended) [A]The chimaeric phage according to [any one of claims 1-6,]claim 1 wherein said proteinaceous molecule comprises a peptide, a protein, or a part, analogue or derivative [thereof] of said peptide or said protein.

8. (Amended) [A]The chimaeric phage according to [any one of claims 1-6,]claim 1 wherein said proteinaceous molecule comprises an antibody, a Fab fragment, a single chain Fv fragment, a variable region, a CDR region, an immunoglobulin or a functional part [thereof]of said Fab fragment, said single chain Fv fragment, said variable region, said CDR or said immunoglobin.

9. (Amended) A chimaeric phage having a coat comprising a mixture of proteins, said mixture of proteins comprising:

a fusion protein wherein a proteinaceous molecule is fused to a phage coat protein, or to a fragment or derivative [thereof,]of said phage coat protein, and wherein said fusion protein is functional so as to render the chimaeric phage infectious, [said mixture further comprising]and

a mutant form of said phage coat protein, wherein said mutant form is characterized in that a phage[,] comprising no wild type phage coat protein from which said mutant form is derived and carrying said mutant form and no copies of said fusion protein[,] is less infectious than a phage[,] comprising no wild type phage coat protein front which said mutant form is derived and carrying in addition to said mutant form at least one copy of said fusion protein.

10. (Amended) [A]The chimaeric phage according to claim 9[,] wherein said mutant form is characterized in that a phage[,] comprising no wild type phage coat protein from which said mutant form is derived and carrying said mutant form and no copies of said fusion protein is non-infectious.

11. (Amended) A chimaeric phage according to [any one of claims 1-10,]claim 1 wherein

said mutant form is further characterized in that a phage[,] having a coat comprising said mutant form in the presence or absence of copies of said functional form[,] is stable.

13. (Amended) A phage collection comprising:

a chimaeric phage according to [any one of claims 1-11]claim 1, or

[an infectious phage according to claim 12]an infectious phage containing at least one copy of a mutant form of a phage coat protein wherein said mutant form has lost the ability to mediate infection of a natural host by said infectious phage.

14. (Amended) [A]The phage collection according to claim 13[,] wherein said phage collection is a phage display library.

15. (Amended) A phage collection consisting essentially of:

the chimaeric phage[s] according to [any one of claims 1-11]claim 1, or

[of]an infectious phage[s according to claim 12]containing at least one copy of a mutant form of a phage coat protein wherein said mutant form has lost the ability to mediate infection of a natural host by said infectious phage.

17. (Amended) [A]The method according to claim 16[,] wherein expression of said fusion protein and/or said mutant form is regulatable by altering the culturing conditions of said host cell.

18. (Amended) [A]The method according to claim 16[or 17,] wherein expression of said fusion protein and/or said mutant form is under the control of a regulatable promoter.

19. (Amended) [A]The method according to claim 16[,] wherein said regulatable promoter comprises the AraC/BAD promoter or a functional equivalent [thereof]of said AraC/BAD promoter.

20. (Amended) [A]The method according to [any one of claims 16-19,]claim 16 wherein said

additional nucleic acid sequence is provided by a helper phage to said host cell.

21. (Amended) [A]The method according to claim 20[,] wherein said helper phage comprises said second nucleic acid.

22. (Amended) [A]The method according to [any one of claims 16-20,]claim 16 wherein said fusion protein and said mutant form are encoded by separate nucleic acids, each comprising a unique selection marker.

23. (Amended) [A]The method according to claim 22[,] wherein said separate nucleic acids each comprise[s] a unique origin of replication.

24. (Amended) [A]The method according to claim 22[or 23,] wherein said separate nucleic acids each comprise[s] codons that essentially do not [render]permit a homologous recombination event between said separate nucleic acids.

25. (Amended) [A]The method according to [any one of claims 16-24,]claim 16 wherein said phage particle [is]comprises:

a chimeric phage having a coat comprising a mixture of proteins, said mixture of proteins comprising:

a fusion protein wherein a proteinaceous molecule is fused to a functional form of a phage coat protein, and

a mutant form of said phage coat protein, wherein said mutant form is characterized in that a phage comprising no wild type phage coat protein from which said mutant form is derived and having a coat comprising said mutant form and no copies of said functional form is less infectious than a phage comprising no wild type phage coat protein from which said mutant form is derived and having a coat comprising said mutant form and at least one copy of said

functional form, [a chimaeric phage according to any one of claims 1-11] or an infectious phage [according to claim 12]containing at least one copy of a mutant form of a phage coat protein wherein said mutant form has lost the ability to mediate infection of a natural host by said infectious phage.

27. (Amended) [A]The helper phage according to claim 26[,] wherein said phage coat protein is the g3 protein.

28. (Amended) [A]The helper phage according to claim 27[,] wherein said mutant form comprises a mutation in the D1 and/or the D2 region of said g3 protein.

29. (Amended) [A]The helper phage according to claim 28[,] wherein said mutation comprises a deletion of substantially all of said D1 and said D2 region of said g3 protein.

30. (Amended) [A]The helper phage according to [any one of claims 26-29,]claim 26 wherein said mutant form is further characterized in that a phage[,] having a coat comprising said mutant form in the presence or absence of a copy of said functional forms[,] is stable.

32. (Amended) [A]The method according to claim 31[,] wherein said other proteins or functional equivalents thereof that are essential for the assembly of said helper phage in said host cell are encoded by said second nucleic acid.

33. (Amended) [A]The method according to claim 31[or 32,] wherein expression of said functional form and/or said mutant form is regulatable by altering the culturing conditions of said host cell.

34. (Amended) [A]The method according to [any one of claims 31-33,]claim 31 wherein expression of said functional form and/or said mutant form is under the control of a regulatable

promoter.

35. (Amended) [A]The method according to claim 34[,] wherein said regulatable promoter comprises the AraC/BAD promoter or a functional equivalent [thereof]of said AraC/BAD promoter.

36. (Amended) [A]The method according to [any one of claims 31-35,]claim 31 wherein said phage coat protein is the g3 protein.

37. (Amended) [A]The method according to claim 36[,] wherein said mutant form comprises a mutation in the Dl and/or the D2 region of said g3 protein.

38. (Amended) [A]The method according to claim 37[,] wherein said mutation comprises a deletion of substantially all of said Dl and said D2 region of said g3 protein.

39. (Amended) [A]The method according to [any one of claims 31-38,]claim 31 wherein said first nucleic acid and said second nucleic acid each comprises a unique selection marker.

40. (Amended) [A]The method according to [any one of claims 31-39,]claim 31 wherein said first nucleic acid and said second nucleic acid each comprises a unique origin of replication.

41. (Amended) [A]The method according to [any one of claims 31-40,]claim 31 wherein said first nucleic acid and said second nucleic acid comprise codons that essentially do not [render]permit a homologous recombination event between said first nucleic acid and said second nucleic acid.

42. (Amended) [A]The method according to [any one of claims 33-41,]claim 33 wherein said helper phage [is a helper phage according to any one of claims 26-30] comprises a nucleic acid encoding phage proteins or functional equivalents of said phage proteins that are essential for the assembly of said helper phage, said nucleic acid encoding phage proteins further encoding a mutant

form of a phage coat protein wherein said mutant form is characterized in that a phage comprising no wild type phage coat protein from which said mutant form is derived and having a coat comprising said mutant form and no copies of a functional form of said phage coat protein is less infectious than a phage comprising no wild type phage coat protein from which said mutant form is derived and having a coat comprising at least one copy of said functional form wherein said functional form is characterized in that it renders a phage particle carrying said functional form in its coat infectious and wherein said helper phage does not comprise a nucleic acid encoding said functional form.

43. (Amended) A method for the enrichment of a first binding pair member in a repertoire of first binding pair members selected from the group consisting of an antibody, an antibody fragment, a single chain Fv fragment, a Fab fragment, a variable region, a CDR region, an immunoglobulin or a functional part [thereof]of said antibody, said antibody fragment, said single chain Fv fragment, said Fab fragment, said variable region, said CDR region, or said immunoglobulin, said first binding pair member being specific for a second binding pair member, comprising the steps of:

contacting a phage collection according to [any one of claims 13-15]claim 13 with material comprising said second binding pair member under conditions allowing specific binding;

removing non-specific binders; and

recovering specific binders, said specific binders comprising said first binding pair member.

44. (Amended) [A]The method according to claim 43 comprising the additional steps of:

recovering from a phage a DNA sequence encoding said first specific binding pair member,

subcloning said DNA sequence in a suitable expression vector,

expressing said DNA sequence in a suitable host, and

culturing said suitable host under conditions whereby said first specific binding pair member is produced.